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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,112	05/13/2002	John A. Heyman	INVITI1220-1	4705

7590 05/10/2004

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EXAMINER	
WILDER, CYNTHIA B	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 05/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No.	Applicant(s)
	09/937,112	HEYMAN ET AL.
	Examiner	**Art Unit**
	Cynthia B. Wilder, Ph.D.	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-33 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-33 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed on March 1, 2004 is acknowledged and has been entered. Claims 1, 4, 9 and 10 have been amended. Claims 8 and 34 have been canceled. Claim 35 has been added. Claims 1-7, 9-33 and 35 are pending. Allowability of claims 8-11 and 32-33 have been withdrawn in view of the new ground(s) of rejections. Accordingly, Applicant's arguments are deemed moot in view of the new grounds of rejections. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office action.

Previous Objections and Rejections

3. The objection to the specification has been withdrawn in view of Applicant's amendment to the specification. The claim rejections under 35 U.S.C. 112 second paragraph have been withdrawn in view of Applicant's amendment to the claims. The prior art rejections under 35 U.S.C. 102(b) have been withdrawn in view of Applicant's amendment of the claims and the new grounds of rejections. The prior art rejections under 35 U.S.C. 103(a) have been withdrawn in view of Applicant's amendment of the claims and the new ground(s) of rejections.

New Ground(s) of Rejections

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1, 2, 5-7, 9, 12, 13, 20, 21, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scheele (US 5,162,209, November 10, 1992) in view of Shuman et al (US 6, 653, 106, effective filing date June 12, 1997). Regarding claims 1 and 35, Scheele teaches a method of producing a full-length coding sequence, said method comprising: synthesizing first strand cDNA using isolated full length mRNA from a population of cells as a template, thereby forming first strand cDNA/mRNA hybrids(s); denaturing the first strand cDNA/mRNA hybrids(s); attaching a non-native tag sequence to the 3' end of the first strand cDNA; and producing a full length double stranded cDNA by synthesizing second strand cDNA using the tagged first strand cDNA produced in the previous step (col. 3, line 60 to col. 5, line 41). The method of Scheele differs from the instant invention in that Scheele does not expressly teach that the non-native tag comprises a recognition site for a site-specific recombinase. In a method of cloning and ligation, Shuman et al teach the use of a tag molecule comprising a recognition site for a site-specific recombinase, wherein said site-specific recombinase is type I topoisomerase, and wherein the method of tagging allows a full length gene sequence to be obtained. Shuman et al teach that the use of a tag molecule, such as, e.g., topoisomerase, comprising a recognition

site for site-specific recombinase is useful because it allows for subsequent insertion of a cDNA molecule into an expression vector (col. 12, lines 6-23, Figure 11 and col. 37, lines 24-45). Shuman et al further teach that a potential advantage of ligation by a site specific recombinase is that the ligation can be targeted by the investigator to RNAs of interest within a complex mixture of RNA molecules (col. 24, lines 17-22). Therefore, one of ordinary skill in the art at the time of the claimed invention would have been motivated to have modified the cloning method of Scheele to encompass a tag comprising a recognition site for a site specific recombinase, such as topoisomerase I. One of ordinary skill in the art would have been motivated to do so for the benefit of subsequent insertion of a cDNA molecule into an expression vector and for the potential advantage of being able to target RNAs of interest within a complex mixture of RNA molecules as taught by Shuman et al.

Regarding claim 2, Shuman et al. teach the method wherein the mRNA is isolated employing an affinity purification material (col. 11, lines 45-56)

Regarding claim 5, Shuman et al. teach the method wherein the mRNA to be isolated comprises a biotinylated cap structure (col. 11, lines 31-44).

Regarding claim 6, Shuman et al. teach the method wherein the affinity purification material is a streptavidin or avidin-complex solid support (col. 11, lines 45-49).

Regarding claim 7, Shuman et al teach the method wherein the mRNA is decapped and dephosphorylated after isolation (col. 11, lines 65-66).

Regarding claim 9, Shuman et al teach the method wherein the tag sequence further comprises a recognition site for a site-specific restriction endonuclease (col. 12, lines 18-21).

Regarding claim 12, Scheele teaches the method further comprising the step of amplifying the cDNA after the producing step (col. 8, lines 58-61).

Regarding claim 13, Scheele teaches the method further comprising inserting the full-length cDNA into an expression vector (col. col. 3, line 65 to col. 4, line 2).

Regarding claims 20 and 21, Scheele teaches the method wherein an isolated full length coding sequence prepared according to the method of claim 1 and a expression vector comprising an isolated full-length coding sequence prepared according to the method of claim 1 (col. 3, line 63 to col. 4, line 2).

7. Claims 1, 2, 5-7, 9, 12, 13, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chenchik et al. (WO 97/24455, July 10, 1997) in view of Shuman et al (6,653,106, November 25, 2003). Regarding claim 1, Chenchik et al teach a method of producing a full-length coding sequence, said method comprising: synthesizing first strand cDNA using isolated full length mRNA from a population of cells as a template, thereby forming first strand cDNA/mRNA hybrids(s); denaturing the first strand cDNA/mRNA hybrids(s); attaching a non-native tag sequence to the 3' end of the first strand cDNA; and producing a full length double stranded cDNA by synthesizing second strand cDNA using the tagged first strand cDNA produced in the previous step (Abstract and page 3, line 29 to page 5, line 35). The method of Chenchik et al differs from the instant invention in that the reference does not expressly teach that the non-native tag comprises a recognition site for a site-specific recombinase. In a method of cloning and ligation, Shuman et al teach the use of a tag molecule comprising a recognition site for a site-specific recombinase, wherein said site-specific

recombinase is type I topoisomerase, and wherein the method of tagging allows a full length gene sequence to be obtained. Shuman et al teach that the use of a tag molecule, such as, e.g., topoisomerase, comprising a recognition site for site-specific recombinase is useful because it allows for subsequent insertion of a cDNA molecule into an expression vector (col. 12, lines 6-23, Figure 11 and col. 37, lines 24-45). Shuman et al further teach that a potential advantage of ligation by a site-specific recombinase is that the ligation can be targeted by the investigator to RNAs of interest within a complex mixture of RNA molecules (col. 24, lines 17-22). Therefore, one of ordinary skill in the art at the time of the claimed invention would have been motivated to have modified the cloning method of Chenchik et al to encompass a tag comprising a recognition site for a site specific recombinase, such as topoisomerase I. One of ordinary skill in the art would have been motivated to do so for the benefit of subsequent insertion of a cDNA molecule into an expression vector and for the potential advantage of being able to target RNAs of interest within a complex mixture of RNA molecules as taught by Shuman et al.

Regarding claim 2, Shuman et al. teach the method wherein the mRNA is isolated employing an affinity purification material (col. 11, lines 45-56)

Regarding claim 5, Shuman et al. teach the method wherein the mRNA to be isolated comprises a biotinylated cap structure (col. 11, lines 31-44).

Regarding claim 6, Shuman et al. teach the method wherein the affinity purification material is a streptavidin or avidin-complex solid support (col. 11, lines 45-49).

Regarding claim 7, Shuman et al teach the method wherein the mRNA is decapped and dephosphorylated after isolation (col. 11, lines 65-66).

Regarding claim 9, Shuman et al teach the method wherein the tag sequence further comprises a recognition site for a site-specific restriction endonuclease (col. 12, lines 18-21).

Regarding claim 12, Chenchik teaches the method of claim 1 further comprising amplifying the cDNA after the producing step (page 13, lines 13- 36).

Regarding claim 13, Chenchik et al. teach the method according to claim 12, further comprising inserting the full-length cDNA into an expression vector (page 14, lines 1-15).

Regarding claims 20 and 21, Chenchik teaches an isolated full length coding sequence prepared according to the method of claim 1 and a expression vector comprising an isolated full-length coding sequence prepared according to the method of claim 1 (pages 4-14).

8. Claims 3, 13-21 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chenchik in view of Shuman et al as previously applied above in view of Carninci et al. (Genomics, Vol. 37, No. 3, pages 327-336, 1996). Regarding claims 3, Chenchik teaches a method of producing a full-length coding sequence, said method comprising: synthesizing first strand cDNA using isolated full length mRNA from a population of cells as a template, thereby forming first strand cDNA/mRNA hybrids(s); denaturing the first strand cDNA/mRNA hybrids(s); attaching a non-native tag sequence comprising a recognition site for a site-specific recombinase to the first strand cDNA; and producing a full length double stranded cDNA by synthesizing second strand cDNA using the tagged first strand cDNA produced in the previous step. Shuman et al. further teaches wherein the mRNA is isolated employing an affinity purification material, wherein said affinity purification material is a streptavidin or avidin-complex solid support. The method of Chenchik in view of Shuman differs from the instant invention in that the referenced do not expressly teach wherein the affinity purification material

comprises one or more cap binding proteins bound to a solid support. Carninci et al teach a method similar to that of Chenchik for producing a full length cDNA molecule, the method comprising: synthesizing a first strand cDNA using isolated full-length mRNA which comprises a biotinylated cap structure, thereby forming a first strand cDNA/mRNA hybrids; denaturing the first strand hybrids and recovering full length double stranded cDNA after RNase I treatment (See entire section entitle "Results" pages 329, column 2 to page 3, column 1, first-fourth paragraphs). Carninci et al. additionally teach wherein the mRNA is isolated employing an affinity purification material comprising one or more cap-binding proteins bound to a solid surface (Abstract). Carninci et al further teach capping the mRNA using a cap-binding structure useful because it selects only for full-length cDNA (Abstract). Therefore in view of the foregoing, one of ordinary skill in the art would have been motivated to have modified the cloning method of Chenchik in view of Shuman et al to incorporate a cap-binding structure for the benefit of specifically selecting only for full-length cDNA as taught by Carninci et al.

Regarding claims 13, Carninci et al. teach wherein the method further comprises inserting the cDNA into an expression vector (page 331, section entitled "Second-strand cDNA synthesis and Cloning" and "Full-length cDNA representation of GAPDH and EF-1-α").

Regarding claims 14 and 15, Carninci et al. teach wherein the method comprises treating the first strand cDNA/mRNA hybrids formed in step (a) with a substance that degrades single stranded RNA; and isolating the under-graded hybrid(s) with an affinity purification material having affinity for capped mRNA prior to performing step (b), wherein said substance is RNase I (see abstract and Figure 1).

Regarding claim 16-18, Carninci et al. teach wherein the mRNA component of the cDNA/mRNA hybrid comprises a biotinylated cap structure and wherein the affinity purification material is a streptavidin complex solid support (page 329, col. 2, section entitled "Biotinylation of Diol Groups of RNA" and abstract).

Regarding claim 19, Carninci et al teach inserting the resultant cDNA strands an expression vector (page 331, sections entitled "Second-strand cDNA synthesis and Cloning" and "Full-length cDNA representation of GAPDH and EF-1-α").

Regarding claims 20 and 21, Carninci et al. teach an expression vector, (Lambda Zap II expression vector) comprising an isolated full-length coding sequence prepared according to the method of claim 1 (page 331, sections entitled "Second-strand cDNA synthesis and Cloning" and "Full-length cDNA representation of GAPDH and EF-1-α").

Regarding claim 30, Carninci et al teach wherein the expression vector is Lambda Zap II expression vector (page 331, section entitled "Full-length cDNA representation of GAPDH and EF-1-α"). Lambda Zap II expression vector id a prokaryotic expression vector. Therefore, the limitation of this claim is inherent in the teaching of the vector by name.

9. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chenchik et al. in view of Shuman as previously applied and further in view of Edery (Molecular and Cellular Biology, Vol. 15, No. 6, pages 3363-3371, June 1995). Regarding claim 4, Chenchik et al in view of Shuman et al teach a method of producing a full-length coding sequence, said method comprising: synthesizing first strand cDNA using isolated full length mRNA from a population of cells as a template, thereby forming first strand cDNA/mRNA hybrids(s); denaturing the first

strand cDNA/mRNA hybrids(s); attaching a non-native tag sequence comprising a recognition site for a site-specific recombinase to the first strand cDNA; and producing a full length double stranded cDNA by synthesizing second strand cDNA using the tagged first strand cDNA produced in the previous step. The references differs from the instant invention in that they do not teach wherein an affinity purification material comprising one or more cap binding proteins selected from the group consisting of eIF4E, eIF4F, eIF4G, nCBP and eIF4E:eIF4G fusion protein is provided. Edery et al. teach a method for producing a full-length cDNA based on an affinity selection procedure using a fusion protein contain the murine cap-binding protein (eukaryotic initiation factor E4) coupled to a solid support matrix, that allows for the purification of MRNAs via the 5' cap structure. The reference teaches when combined with a RNA digestion step, specific retention of complete/RNA duplexes following first strand synthesis is achieved (see abstract). Edery et al teaches that the use of the cap binding protein, eukaryotic initiation factor E4 is advantageous because this protein shows string binding specificity for methylated cap structures of eukaryotic mRNAs (pages 3363, col. 2, first full paragraph). Therefore, in view of the foregoing, one of ordinary skill in the art would have been motivated at the time of the claimed invention to have modified the cloning method of Chenchik et al. in view of Shuman et al to encompass a cap-binding protein such as eIF4E because of the advantages taught by Edery that cap-binding proteins such as eIF4E have strong binding specificity.

10. Claims 21-24 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chenchik in view of Shuman et al and Carninci et al. as previously applied and further in view of Sambrook et al. (Molecular Cloning, A laboratory Manual, Second Edition, Cold Spring Harbor

Laboratory Press, 1989). Regarding claim 21-24, 30, Chenchik in view of Shuman et al and Carninci et al. teach an expression vector comprising an isolated full-length coding sequence prepared according to the method of claim 1. Carninci et al further teach wherein the expression vector is a bacteriophage lambda Zap II expression vector. The references do not expressly teach the elements of the expression vector. However, the elements of the lambda Zap II vector is taught in general laboratory manual by Sambrook et al. Sambrook et al disclose the characteristics of the lambda Zap II vector and elements that the vector comprises therein. These include a T7 promoter-enhancer, a selection marker encoding a protein which imparts antibiotic resistance to cells and an origin of replication (see pages 2.53 and 2.54). Sambrook et al teach that the vector is useful because expression of fusion proteins and production of capped RNA transcripts are readily obtainable (page 2.53, first paragraph). Therefore in view of the foregoing, one of ordinary skill in the art would have been motivated to utilize a Lambda Zap II expression vector comprising the isolated full-length coding sequence prepared by the method of claim 1 for the advantages taught by Sambrook that the Zap II vector is useful because expression of fusion proteins and production of capped RNA transcripts can be readily obtainable.

Regarding claim 31, Sambrook et al. teach an expression vector according to claim 30, wherein the eukaryotic expression vector is pMT expression vector (see 16.20 last paragraph and 16.22, entire page).

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11. Claims 26 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chenchik in view of Shuman et al and Carninci et al as previously applied and further in view of

Jacobs, Jr. et al (US 5,981,182, filing date March 13, 1997). Regarding claim 29, Chenchik in view of Shuman et al and Carninci et al. teach an expression vector comprising an isolated full-length coding sequence prepared according to the method of claim 1. Carninci et al further teach wherein the expression vector is a bacteriophage lambda Zap II expression vector. The references do not expressly teach wherein the vector comprises a polypeptide encoding sequence which includes an intein encoding sequence. Jacobs, Jr et al teach vector constructs for the selection and identification of open reading frames. Jacobs. Jr et al teach wherein the vectors may comprise a pBluescript II or lambda Zap II vector (col. 7, lines 12-18) and wherein the vector may comprise a polypeptide encoding sequence which includes an intein encoding sequence (col. 5, lines 17-23). Jacobs, Jr. et al further teach that an intein is a protein sequence which, during protein splicing, is excised from a protein precursor (col. 5, line 17-20). The reference further teaches that vectors constructs comprising inteins are unique in that that they utilized the protein splicing properties of the inteins which is useful for the identification of potentially protective antigens of a pathogen (col. 10, lines 42-65). Therefore, in view of the foregoing, one of ordinary skill in the art at the time of the claimed invention would have been motivated to have provided an expression vector comprising an intein encoding sequence in the cloning methods of Chenchik et al, Shuman et al. and Carninci et al. One of ordinary skill in the art would have been motivated to do for the unique protein splicing properties of inteins as taught by Jacobs, Jr. et al.

12. Claims 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chenchik in view of Shuman et al. and Carninci et al. as previously applied and further in view of Elledge

et al. (US 5,851,808, December 22, 1998). Regarding claims 26-28, Chenchik in view of Shuman and Carninci et al. teach an expression vector comprising an isolated full-length coding sequence prepared according to the method of claim 1. Carninci et al further teach wherein the expression vector is a bacteriophage lambda Zap II expression vector which is capable of expressing fusion proteins. The references do not teach wherein the expression vector comprises a glutathione-S-transferase polypeptide or a polyhistidine tract. In a general reference, Elledge et al teach rapid subcloning using site-specific recombination. Elledge et al teach an expression vector (pHOST vector) which have been modified by the insertion of a sequence-specific recombinase target site. The reference further teaches wherein the vector may encode a protein domain such as an affinity domain including, but not limited to, glutathione-S-transferase, a polyhistidine tract and etc. (col. 16, lines 50-62). The reference teaches that the vector is useful because it permits the rapid exchange of an entire cDNA library to a variety of expression vectors (col. 18, lines 38-42). Therefore, in view of the foregoing, one of ordinary skill in the art would have been motivated to have modified the expression vector of Chenchik et al in view of Shuman. and Carninci et al to incorporate a glutathione-S-transferase polypeptide and a polyhistidine tract as taught by Elledge et al for the benefits of providing an expression vector which permits the rapid exchange of an entire cDNA library to a variety of expression vectors as suggested by Elledge et al.

Claims 10, 11, 32 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chenchik et al. in view of Shuman as previously applied and further in view of Zhang et al (Journal of Biological Chemistry, Vol. 27, No. 40, pages 23700-23705, October 6, 1995).

Regarding claims 10, 11, 32 and 33, Chenchik et al teach a method of producing a full-length coding sequence, said method comprising: synthesizing first strand cDNA using isolated full length mRNA from a population of cells as a template, thereby forming first strand cDNA/mRNA hybrids(s); denaturing the first strand cDNA/mRNA hybrids(s); attaching a non-native tag sequence to the 3' end of the first strand cDNA; and producing a full length double stranded cDNA by synthesizing second strand cDNA using the tagged first strand cDNA produced in the previous step (Abstract and page 3, line 29 to page 5, line 35). The method of Chenchik et al differs from the instant invention in that the reference does not expressly teach that the non-native tag comprises a recognition site for a site-specific recombinase. In a method of cloning and ligation, Shuman et al teach the use of a tag molecule comprising a recognition site for a site-specific recombinase, wherein said site-specific recombinase is type I topoisomerase, which has binding affinity for the first strand of a duplex DNA molecules, and wherein the method of tagging allows a full length gene sequence to be obtained. Shuman et al teach that the use of a tag molecule, such as, e.g., topoisomerase, comprising a recognition site for site-specific recombinase is useful because it allows for subsequent insertion of a cDNA molecule into an expression vector (col. 12, lines 6-23, Figure 11 and col. 37, lines 24-45). Shuman et al further teaches wherein full-length mRNA is isolated employing an affinity purification material comprising a streptavidin or avidin complex to a solid support (col. 11, lines 45-49). The reference of Chenchik et al in view of Shuman et al differs from the instant invention in that the references do not teach wherein the tag sequence, which comprises a site-specific recombination sequence, is attached by *E. coli* topoisomerase III. Zhang et al provides a general teaching of the mechanism of action of *E. coli* topoisomerase III. Zhang et al disclose

that *E. coli* topoisomerase III is a cleavage site-specific protein (page 23702 col. 1, first full paragraph) that has a strong binding affinity for small, single-stranded DNA with a relatively low affinity for double stranded DNA (page 23704, col. 2, third paragraph from bottom of col. 2). Therefore, in view of the foregoing, one of ordinary skill in the art would have been motivated to have modified the cloning method of Chenchik et al. in view of Shuman et al. to encompass *E. coli* topoisomerase III instead of topoisomerase I as taught by Shuman et al. for it's strong binding affinity for small, single stranded DNA molecules.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Cynthia Wilder

CYNTHIA WILDER
PATENT EXAMINER
5/5/2004